# Exhibit 2

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 10-2734 (CCC/JAD)

IN RE BIOGEN '755 PATENT LITIGATION

DEPOSITION OF DR. JEFFREY V. RAVETCH

Washington, D.C.

August 30, 2011

Reported by: Mary Ann Payonk, RDR-CRR

Job No. 41405

August 30, 2011

9:30 a.m.

Deposition of DR. JEFFREY V. RAVETCH, held at the offices of Williams & Connolly, 725 Twelfth Street, N.W., Washington, D.C., pursuant to Notice before Mary Ann Payonk, a Certified Realtime Reporter and notary public of the District of Columbia.

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used in a variety of clinical studies.

Q. I understand. But we are discussing the citations that appear in the '755 patent which you said that you have reviewed, at least some of them.

My question for you is: Those studies that you reviewed that appear in the '755 patent, the interferon that was used to treat humans, was that -- was that native beta interferon or recombinant beta interferon?

A. So, once again, I would have to have the reference or -- to answer your questions accurately; otherwise, I'd just be relying upon my memory.

Q. Do you have any recollection sitting here today as to the purity of the beta interferon that was used to treat human patients and described in the papers which are cited in the '755 patent?

A. Be the same answer, counselor. I would need to review the particular publication to answer the question as to the degree of purity of a particular preparation that might have been used.

Q. And sitting here today, you don't have any idea as to how pure those -- those preparations were?

A. I don't have a distinct recollection. They were degrees of purity. In fact, the patent itself describes the -- the range of purity in column 4, for example. They talk about purity of 50 percent yields, 100 percent yields at specific activities of -- ranging from 10 to the 4th to 10 to the 9th units per milligram. So there's a -- certainly a large range that is summarized in the patent.

So for any particular reference, I would need to refer to that reference to answer your question.

Q. I want to turn your attention to the discussion of genetic engineering, which I believe you mention at approximately paragraph 21. Are you there?

A. Yes.

Q. Paragraph 21, you state that -- let me make sure that I read this correctly -- you say there, "By The late 1970s, a variety of experimental techniques converged and gave rise

to the field of genetic engineering."

It continues. Last paragraph is, "The recombined human and plasmid DNA could then be reintroduced into bacteria. This process of introducing foreign DNA into a bacterial cell is referred to as transformation." Do you see that?

A. Yes, I do.

Q. The term "transformation" as it was understood in the -- the late 1970s, did that require that the foreign DNA be incorporated into the chromosome of the host?

A. No, it did not. The term "transformation" is a term that developed from bacterial genetics and is one of the three mechanisms by which DNA can be transferred into a bacterial cell, the other two being conjugation and transduction.

In each case, the presence of the DNA is detected by its phenotypic characteristics, how it modifies the cell, conferring the particular selectable or screenable marker.

In the case of transformation, it's naked DNA and the process leads to a stable

phenotype in order to be detected through multiple generations of growth. That stable phenotype does not require integration into the chromosomal DNA but it does require stable propagation of the introduced DNA.

Q. Paragraph 22, "Because the transformed bacteria now contain the human DNA sequence, it could transcribe that sequence into mRNA and translate that sequence into a polypeptide. Using this process, the scientist could cause bacteria to make a polypeptide previously only made in human cells." Do you see that?

A. Yes, I do.

Q. What would the results be if the human gene that were inserted into the bacteria contained introns?

MR. BERL: Objection.

A. If the human DNA had intervening sequences, those sequences would be transcribed, assuming that there is a -- a correct transcription initiation sequence that's recognized by a bacterial polymerase either because of its integration into the

chromosome or by virtue of providing such a transcription initiation sequence on the -- the autonomously replicating plasmid --

THE REPORTER: On the?

A. On the autonomously replicating plasmid, and that DNA sequence would be treated like the bacterial host DNA as a template for RNA polymerase to generate a transcript.

Q. And would that -- would that then be translated into a polypeptide?

A. So there too it would depend upon whether the DNA sequence that was inserted either on a plasmid or in the chromosome was in the correct configuration so that it is able to be recognized by the initiation of ribosome binding and translation used in the translational machinery of the bacterial cell to initiate a -- a polypeptide that would read from the RNA strand.

In that case, either a fusion protein to a bacterial coding region or to -- or in the absence of a translational effusion, a de novo translation product as a polypeptide would be generated until which case a termination codon

was able to terminate translation.

Q. Now, do -- do procaryotic cells, bacteria, for example, do they have the endogenous mechanisms to splice out introns?

A. That's a very complicated question, counselor. The procaryotic cells represent a very large kingdom, and there are members in that kingdom which have interrupter genes in which splicing of a sort occurs.

I would rather not go into the specific details of how those various systems differ because it is a world of complexity. So the answer to your question is in some circumstances, it does happen.

Q. That's fair. Let's try confining the question, then, to bacteria.

A. Same answer.

Q. All right. So there are bacteria that you believe do have mechanisms by which they can process and remove introns?

A. There are bacteria that have interrupter genes, and in those bacteria there are examples of -- of a processing event that occurs. If you restrict it to E coli, where we

have not seen evidence of that, the answer would be a little easier.

Q. We -- we're getting there.

A. Thank you.

Q. Working our way down.

In the case of E coli, does E coli have the endogenous mechanisms required to splice or to remove introns?

A. So I think the key in your question is endogenous mechanisms. Right. One can engineer E coli to do almost anything you want --

Q. Understood.

A. -- but endogenously, E coli, to my understanding, does not process intervening sequences.

Q. And as such, if one wanted to express a human gene in E coli that had not been otherwise modified, and the human gene contained intervening sequences, one would have to remove those prior to insertion into the E coli; correct?

MR. BERL: Objection.

A. So the -- as I mentioned in paragraph

21, the technology for doing that was -- was well developed. I was doing it in the NIH in Phil Leder's lab. It involved isolating the -- the processed messenger RNA and not using the chromosomal DNA as your source of the genetic information for the gene of interest. And using the spliced RNA as a cDNA copy in most cases avoided that complication. And those were techniques that had been developed in the mid to late '70s.

Q. So that would be yes?

MR. BERL: Objection. You can answer.

A. The answer is what I gave you.

Q. So one would remove or use cDNA in which the intervening sequences had already been removed if one wanted to express that DNA or cDNA in a bacterial cell?

MR. BERL: Objection.

A. That's one approach. I said there are a variety of techniques that have been developed.

One popular and common one was to use cDNA derived from a processed mRNA from a

eukaryotic cell. In many cases, the eukaryotic gene lacked introns, in which case there was no such concern. Many of the early studies in yeast, for example, studies that we did in malaria parasites, for example, other protozoans, lacked intron-containing genes in each case, chrysophilized (ph) L intron containing genes. So in many cases, it was unnecessary. But in cases where it was a -- a consideration, the techniques had been developed to do that.

Q. Proteins expressed in E coli are not glycosylated; is that correct?

MR. BERL: Objection.

A. I -- I'll qualify it for you. In the unmodified E coli, there are E coli strains that have been modified to glycosylate; however, in the -- the unmodified E coli, glycosylation does not occur. On -- sorry. Protein glycosylation of the sort that we see in eukaryotic cells does not occur. There is a glycosylation, of course, that occurs on the cell wall which is quite important to the bacterial survival, but it's a different type

of pathway.

Q. Understood.

Just out of curiosity, you -- you mentioned that E coli had been modified so that they can glycosylate. When was the first time you were aware of E coli being developed that could glycosylate a protein?

A. So it's not -- so it's not a question that I've researched thoroughly. I'm certainly aware of the more recent work because it impinges on my own studies. And strains of coli have been developed that have the glycosylation machinery for human glycant structures. But I can't answer your question in terms of a -- a thorough review as to when such were first developed.

Q. Did such E coli exist in 1980?

A. I can't answer the question. I haven't reviewed the literature with that issue in mind.

Q. Do you have any reason to believe that E coli that were capable of -- that had been modified such that they were capable of glycosylating proteins existed in 1980?

MR. BERL: Objection.

A. It was a very important field, then and today, and many people were actively involved in studying glycosylation of proteins, polypeptides, so that it wouldn't surprise me if there were some studies that were done in the early '80s. But I don't have a definitive date I can give you.

THE WITNESS: Wonder if we can take a break shortly. I've run out of water. It's been about an hour.

MR. SANDEL: Sure. Of course we can take a break.

THE WITNESS: Now would be a good time?

MR. SANDEL: Off the record.

THE VIDEOGRAPHER: Here marks the end of videotape number 1 taken in the deposition of Dr. Jeffrey Ravetch. The time on the video screen is 10:47 and 46 seconds.

(A recess was taken from 10:47 a.m. through 10:47 a.m.)

THE VIDEOGRAPHER: Here marks the

beginning of videotape number 2 taken in the deposition of Dr. Jeffrey Ravetch. Going back on the record. The time on the video screen is 10:48 and 44 seconds. Please continue.

BY MR. SANDEL:

Q. Welcome back, doctor.

A. Thank you.

Q. Just let me ask you, as of 1981, how many recombinant human proteins had been produced?

MR. BERL: Objection.

Q. You may find it helpful to refer to page -- or, sorry, paragraph 24 of your report.

A. Thank you. I was looking for that.

MR. BERL: Objection. Since it's colloquy, can you repeat the question?

(The reporter read from the record.)

A. So in paragraph 24 of my report, I summarize the published reports of expression of various recombinant polypeptides in nonhuman cells. And of the published reports of -- of human proteins -- human polypeptides, excuse me, in -- as recombinant molecules, I count

about a half dozen in the exhibits I provided from 5 to 21.

I'm aware of additional ones that were either not published, that was work in progress. Our own work, for example, on the human immunoglobulins didn't lead to published reports per say because they were part of the research program to develop various molecules that we use as probes to make antibodies and so forth.

So I think the estimate of a half dozen of published reports would probably indicate that at least two or three times that number were in common usage by the molecular biology community.

BY MR. SANDEL:

Q. Let's start with the ones that were published that you cite. So human growth hormone is a human polypeptide; correct?

A. Human growth hormone is a human polypeptide, yes.

Q. And that was expressed in recombinant form?

A. That was expressed in recombinant

form, that's correct as well.

Q. And the paper describing that is Exhibit 10 to your report; correct?

A. That's one of the reports.

Q. Published in Nature in October 1979?

A. That's reference -- Exhibit 10 of my report, that's correct. There's another report under tab -- Exhibit 13 of human growth growth hormone expression of bacteria that is a -- a Nature paper from 1979, August of '79 of the -- different --

Q. I'm sorry --

A. -- group.

Q. -- doctor, do you mean a Science publication?

A. I'm sorry. Science publication, yes, it's a Science publication, yes, Science publication, August of '79 from Howard Goodman's group.

Q. It's not a statin. Is that a human protein?

A. It's a polypeptide.

Q. Polypeptide?

A. It's a human polypeptide.

Q. And is that produced in recombinant form?

THE REPORTER: Sir, repeat.

Q. Strike that. Was somatostatin produced in recombinant form?

A. Somatostatin --

Q. Doctor --

A. Yes? Which tab is it? The question is where. I'm looking for the reference, to be precise.

Q. I think it was actually Exhibit 12.

A. Yes. Exhibit 12 is a Science publication, Expression in E coli of a Chemically Synthesized Gene for the Hormone Somatostatin. And that's a study that I believe came from the Riggs Itukara group.

Q. And interferon alpha had been expressed in recombinant form; is that correct? Point you to Exhibit 15.

A. Leukocyte interferon or interferon alpha, yes, Exhibit 15. And that's a -- a publication in Nature -- Nature right, in 1980, yes, March of 1980.

Q. And beta interferon had been

expressed as a recombinant protein, had it not? And let me direct to you Exhibit 25 of your report.

A. September 1980 publication from Fiers in Nature describes the expression of human fibroblast interferon gene in E coli. And there are a few other publications relevant to that as well. Exhibit 26 and 27 describe -- and 28 all describe other groups who generated beta interferon as -- in recombinant form in E coli, for example. I believe insulin as well was a human polypeptide that was expressed in E coli as a recombinant molecule.

Q. Now, the publications describing the -- the production of recombinant human growth hormone, somatostatin, alpha interferon, and beta interferon were all published in -- in prestigious journals; correct?

A. Yes. I say that because I publish in those journals.

Q. How would you characterize Nature amongst journals in terms of prestige?

A. It -- it's very subjective. You know, like I said, it's a journal that many of

macrophage," and it continues from there. Do you see that?

A. I do --

MR. BERL: Objection.

A. -- see those words.

Q. All right. Would you turn to the summary of the invention, which appears in column 3?

A. Yes.

Q. Starting at line 14, your patent specification states "The invention also provides a cell line capable of stably expressing an FC receptor protein which is expressed on NK cells." Do you see that?

A. Yes, I do.

Q. Okay. Is that -- the cell line that you're referring to in the summary of the invention, is that the host cell that you refer to in the claims?

MR. BERL: Objection.

A. As I said, counselor, in the absence of being able to review not just the -- the patent that you've given me but the file history, I couldn't comment on what had

occurred in the Patent Office that led to the specific language of different claims.

Q. Do you have a reason to believe that a -- a host cell comprising a recombinant cloning vehicle is not adequately described as a cell line capable of stably expressing an FC receptor which is expressed on NK cells?

MR. BERL: Objection.

A. I have no opinion one way or the other.

Q. So what's your current understanding of host cell in the claim of your patent?

MR. BERL: Objection, calls for a legal conclusion.

A. I -- I have no current understanding of the claims of this patent. As I understand, and the reason why we're here today, is to offer opinions regarding the claim construction of the '755 patent. And, I mean, claim construction is a matter for the Court to determine. I can offer my scientific opinion, and that has to be based on a review of all the pertinent information, including the file history. So unless I can see a file history

and understand something, I can't even offer my scientific understanding of what may have occurred to generate a particular claim term. Even with that, it's still a matter for the Court to decide.

Q. I understand.

And I'm asking your scientific opinion as to one of the skill in the art reading your patent would understand that a host cell could also be described as a cell line that's capable of stably expressing a recombinant protein.

MR. BERL: Objection.

A. I'm not going to be able to answer your question. I've given you the reason why I can't answer it. I have the opportunities to review not just the '755 patent but the file history, which as you hopefully will get to, influenced my opinion as to the scientific understanding of one of skill in the art as to what some of the terms may mean. In the absence of similar ability, I can't opine on the meaning of claim terms in the '031 patent.

Q. All right. So -- so you yourself as

the inventor of the patent sitting here today cannot provide an opinion as to what your patent means --

MR. BERL: Objection.

Q. -- what the patent means; is that right?

MR. BERL: Objection.

A. In the absence of being given the opportunity to review the information I asked for, I will not be able to provide you with the opinion sitting here today for this -- this patent, these claims.

MR. SANDEL: Fair enough. Go off the record.

THE VIDEOGRAPHER: Going off the record. The time on the video screen is 12:26 and 18 seconds.

(A luncheon recess was taken from 12:26 p.m. through 1:23 p.m.)

- AFTERNOON SESSION -

THE VIDEOGRAPHER: Going back on the record. The time on the video screen is 13:23 and 4 seconds. Please continue.

J. Ravetch

BY MR. SANDEL:

Q. Welcome back. I trust you had a pleasant lunch.

A. Yes, I did. Thank you.

Q. Would you turn to -- you still have Exhibit 1 before you?

A. Yes, I do.

Q. All right. Would you turn to tab 3 or Exhibit 3 of your expert declaration? That's the '755 patent. And turn to Claim 1, which appears at the back of the patent.

A. I have it.

Q. And in the first indented paragraph of Claim 1 is the phrase "produced by a nonhuman host, transformed by a recombinant DNA molecule." Do you see that?

A. Yes.

Q. Do you believe that one of skill in the art in 1980 -- strike that.

Do you believe that in 1980, that phrase would be commonly understood by one of skill in the art?

A. I believe one of skill in the art would understand that phrase to refer to a

process of making a recombinant polypeptide.

Q. Let's take that in baby steps first.

A. Okay.

Q. Do you -- do you understand that in 1980, that phrase would be commonly understood by one of skill in the art?

A. I'm not -- I'm not quite sure what you mean by "commonly understood." I think the words do speak for themselves, and they describe a process, or several processes.

Q. So take this in little steps. So correct me if I'm wrong. So yes, you believe that that phrase would be commonly understood by one of skill in the art in 1980?

MR. BERL: Objection.

A. I'm -- I'm not quite sure what you mean by "commonly understood by one of skill in the art in 1980." I think one of skill in the art reading this part of the claim would have an understanding as to what that means, and it refers to process steps.

Q. Haven't quite gotten to what they would understand it to be yet, so try to take this in baby steps. They would understand the

meaning of the term.

A. Terms, terms.

Q. Right.

A. One of skill --

Q. Terms, right.

A. -- in the art would understand the words in that part of the claim, and I offer my opinion as to what I believe they would understand those terms to mean.

Q. And the meaning of that -- so you offer a -- an opinion as to how they would understand that. Is -- is that influenced by the context in which it appears in Claim 1?

A. I believe it's understood in the context of the entire patent and its specification and the file history.

Q. So let's start by, standing alone, just the term "produced by a nonhuman host, transformed by a recombinant DNA molecule," just that term, all right, would that term have a commonly understood meaning in 1980?

A. I think that term -- you'd -- you'd have to show me how that term was being used, in what application, to understand anything

beyond what I've said. I think the words have distinct meaning, and the distinct meaning is informed in this particular case by what's in the patent and in the file history and what one of ordinary skill in the art would understand.

Q. Let's talk about that, then. Now, in your report -- sorry, declaration, paragraph 35, you say that "The requirement of the recombinant polypeptide be produced by a nonhuman host does not in any way define the structure of the recombinant polypeptide. The requirement that the nonhuman host be transformed by a recombinant DNA molecule likewise does not define the structure of the recombinant polypeptide." Is that right?

A. That's correct.

Q. All right. And that's the opinion you hold here today?

A. Yes, it is.

Q. And I should have done this earlier, and I'm sorry for not. The -- the opinions set forth in your declaration, do those represent your current opinions?

A. Yes, they do.

J. Ravetch

Q. All right. You haven't had any occasion to alter or change those opinions since this report was drafted and submitted?

A. That's correct.

Q. And do the opinions expressed in this report accurately represent the opinions you would provide were you asked to testify at trial or at a hearing?

MR. BERL: Objection. You can answer.

A. The opinions I express in this report in relation to the particular matters I've been asked to address are the opinions that I would express in court if asked to testify.

Q. Now, tell me, why doesn't the -- the requirement that the recombinant polypeptide be produced in nonhuman host in any way define the structure of the recombinant polypeptide?

A. As I explain in other parts of my report, the -- the recombinant polypeptide is the product of gene expression, and that is dictated by the recombinant DNA molecule that is provided, because a recombinant polypeptide is a linear sequence of amino acids. So the

host and the method of production, the method of transformation, do not affect the linear array of amino acids dictated by the DNA molecule.

Q. Do the host, the method production, the method of transformation, do any of those affect the three-dimensional structure of the polypeptide?

MR. BERL: Objection.

A. By definition, the polypeptide has been defined with -- in the patent and, I believe, by the parties involved as the linear array of amino acids dictated by the codon sequence. And I think that therefore is not -- let me go back to the patent, '755, column 8, under line 62. "Polypeptide: A linear array of amino acids connected one to the other by peptide bonds between the alpha amino and carboxy groups of adjacent amino acids." By definition, a linear array is not a three-dimensional structure.

Q. So let's step away from that a second and let's talk about the -- polypeptides as they exist in nature or in culture or are used

in clinical treatment have a three-dimensional structure, do they not?

A. Counselor, the claim is defined -- the claim term is defined by the patent, and I have been asked to apply the claim -- interpret the claim terms in late of the patent specification.

If the patent says it's a linear array of amino acids, then it's a linear string of amino acids, you know. Whether or not you can find a situation where a polypeptide may or may not have a secondary or even tertiary structure is beside the point because I'm following the instructions that I have been given to understand the claim in light of the specification and the file history, and there, it's very clear what a polypeptide is. And it's also the accepted definition of a polypeptide.

Q. Would the host cell influence the -- the glycosylation of the recombinant polypeptide?

MR. BERL: Objection.

A. Once again, the recombinant

polypeptide is specified by the DNA codon, DNA sequence, which is transcribed into an RNA, and the codons specify the polypeptide. That's the beginning and end of the definition of polypeptide. What happens subsequently to the polypeptide is no longer a polypeptide.

Q. How would you describe what happened subsequently, the product of -- what does a polypeptide become subsequently?

A. Becomes a protein.

Q. All right.

A. Polypeptide chains can assemble into a protein. I'll give you an example. We refer to hemoglobin as a protein. It's composed of four polypeptide chains. Each chain has a particular structure that occurs after the polypeptide has been synthesized in the cell or however else you are making it. So a polypeptide both in the patent and as molecular biologists understood it because of the universality of genetic code is specified by the DNA as a linear array of amino acids.

Q. And in the case of hemoglobin you mentioned, are any of the four polypeptides

glycosylated?

A. I don't recall. I don't believe they are. I would have to review that. It's been a while since I've been asked to think about hemoglobin or any other posttranslational modification that might occur.

But I think I -- I very clearly say in the -- in my introduction, my background section, when I talk about how polypeptides are made, in paragraph 18: "After expression, the cellular machinery for assembling polypeptides releases the two molecules, the RNA and the polypeptide, and each gene -- each goes its separate way, the mRNA to be degraded or to direct the synthesis of another copy of the polypeptide, the polypeptide to be processed and folded and put to work as a protein."

Q. So let me understand this, then. If a polypeptide -- in your opinion, if a polypeptide is glycosylated, it is no longer considered a polypeptide?

A. You might refer to it as a glycosylated polypeptide. You might refer to it as a protein precursor. You might refer to

it as any of a number of terms. But when you define the term "polypeptide," as the patent has done quite explicitly, I don't think there's any real room for redefining it as something else. It is a linear sequence of amino acids.

Q. Doesn't say whether the -- the definition doesn't say whether it's glycosylated or not, does it?

A. The definition -- the definition says it's a linear sequence of amino acids. It does not incorporate any changes beyond the amino acids. What occurs to the amino acid subsequently is not part of the linear sequence of amino acids. That's specified by the DNA molecule, for now the third --

Q. That definition --

A. -- time.

Q. -- you just read doesn't preclude glycosylation, does it?

A. Yes, it -- yes, it does. Yes, it does. Because then, you would not refer to a linear sequence of amino acids, you would say -- if, in fact, you wanted to invent a new

definition for polypeptide, you would say it's a linear sequence of amino acids that are posttranslationally modified by the following, on and on and on. Doesn't say that because that's not correct.

What is technically correct is a linear sequence of amino acids means exactly what the words say: Amino acid coupled to amino acid, alpha, carbon to carboxy terminus, peptide --

THE REPORTER: Carbon? Carboxy?

THE WITNESS: Terminus.

THE REPORTER: Thank you.

A. Forming peptide bonds.

Q. And as soon as that folds in any way and -- and it's no longer linear, it's not a polypeptide, in your opinion?

MR. BERL: Objection.

A. Linear does not refer to a structure. All right? You're -- you're confusing the notion that some kind of a collagen strand can be a linear protein. We don't mean linear in a structural sense. We mean the sequences of amino acids as arrayed as if you were writing

them on a line. That's what linear means. A linear sequence of amino acids. So the polypeptide is no more, no less than the precise amino acid sequence specified by the DNA.

Q. But it does exist in a physical form, does it not?

A. During the -- well, during the translational process, there is a nascent polypeptide which grows off the ribosome. Right? And then events occur, sometimes co-translationally, sometimes post-translationally, to the polypeptide chain as the protein folding and modifications occur. So that's why we have to define the polypeptide as just the amino acid sequence. No more, no less. That's what it is. And that we know comes from the DNA sequence which is embodied in genetic code which is, with a few exceptions, universal.

Q. Now, different hosts will process that, as you say, nascent polypeptide, in different ways; is that correct?

A. They can. It's not a hard-and-fast

rule.

Q. No, I understand. But they can.

A. If it's made in E coli and the polypeptide has a glycosylation signal, glycosylation will not occur. E coli doesn't glycosylate. Other cells have other types of modifications that can occur to the polypeptide, but the polypeptide is the same. You haven't changed the polypeptide.

How you express it and what kind of cell, how that cell was transformed, in no way defines the polypeptide. That is purely and simply defined by the DNA sequence.

Q. Now, how would one administer a polypeptide to a patient?

MR. BERL: Objection.

A. First of all, the claim calls for administering to a patient in need of such treatment a therapeutically effective amount of a composition comprising a recombinant polypeptide. Right? So the amino acid sequence is clearly a component of the preparation because it is the basis for the potentially ultimate protein product which

might be administered. But you start with the polypeptide. That is defined by the DNA sequence, so you're -- you're starting to define the amino acid sequence, and that is -- and that is later on defined by the claim in the top of column 50 of -- by the DNA sequences.

So the DNA sequences that are claimed in this particular invention, alleged invention, are specified by the DNA sequence, and they are part of the composition. Other things can be added to it, certainly the case, but the composition is the DNA sequence plus other things.

Q. If I understood you earlier -- and please correct me if I misunderstood -- you said that a polypeptide, if it were a glycosylated or modified in any way, is no longer a polypeptide.

MR. BERL: Objection. He clarified that multiple times.

A. Right. So -- so I -- once again, the claim reads "recombinant polypeptide."

"Recombinant" has a meaning. Right?

"Recombinant" tells you that it's been expressed in a nonnatural host. Right. So the rest of the claim offers nothing more to the definition of "recombinant polypeptide."

If I express a polypeptide in a particular cell, other things can happen to it or not happen to it. The polypeptide is the amino acid sequence specified by the DNA as claimed in the '755 patent.

The fact that it's recombinant tells you that it's been expressed in a variety of different nonnatural cells. Right? So the rest of the claim term would have no meaning if it -- all it did was reiterate recombinant. Its meaning is to provide you with how you've done that. And it tells you how you've done that because you've produced it through a process in a nonhuman host, and that host had been transformed by a recombinant DNA molecule.

So the process is laid out for the production of the recombinant polypeptide. That's the way I understand the claim, and I believe that's the way the inventors understood the claim.

Q. Why do you believe that that's the way the inventors understood the claim?

A. Because they tell you in their patent, as we talked about before, in the abstract and, for example, in the top of column 6, that the expression of these recombinant molecules is the invention. It is a method of making this which is the invention, to then be used for different applications, including the treatment of patients in need of a therapeutic administration.

Q. Well, you'll agree with me that Claim 1 is clearly directed to a method for immodulation or treating a viral condition, disease, cancer or tumors comprising the step of administering to a patient in need of such treatment a therapeutically [sic] amount of a composition"; correct?

MR. BERL: Objection.

A. Produced in a particular way --

Q. I understand --

A. -- so you -- counselor --

Q. I understand.

A. So you --

J. Ravetch

THE REPORTER: Gentlemen?

A. Let me finish. You can't remove that from the claim. I'm sorry. It's in there. And I understand it to have meaning. And the meaning I have it -- I understand it to have is a method by which you've made that recombinant polypeptide.

Yes, it is a -- the intent of the claim is to, as the preamble lays forth, is to treat by administering something made in a certain way. So all of that is part of the claim. Treat, with something, made in a particular way. That's my opinion of the claim meaning.

Q. Now, in your declaration you refer to statements that were made in the prosecution history beginning at paragraph 38 and continuing through. You see that?

A. Yes, I do.

Q. Paragraph 39 says, "During the prosecution of the '755 patent, the examiner described the following two claims as containing the same actual process steps and positive process steps." And then there is a

table presenting two claims. Are these claims from the '755 patent file history?

A. I would need --

MR. BERL: Objection.

A. I would -- I would need to actually look at the actual cite in the brief.

MR. BERL: You -- and we served a -- an amended corrected version I'm. Not sure why you're using this preamended corrected version of the declaration.

MR. SANDEL: I don't recall receiving a corrected version. Do you have a copy?

MR. BERL: Yeah, in the other room.

MR. SANDEL: Would you mind getting one for us?

MR. BERL: Sure.

MR. SANDEL: Go off the record for a second.

THE VIDEOGRAPHER: Going off the record. The time on the video screen is 13:48 and 28 seconds.

(Discussion held off the record.)

J. Ravetch

THE VIDEOGRAPHER: Going back on the record. The time on the video screen is 13:51 and 10 seconds. Please continue.

(Exhibit No. 6 was marked for identification.)

BY MR. SANDEL:

Q. Let me hand to you what has been marked as Exhibit 6, and it is titled "Declaration of Dr. Jeffrey V. Ravetch in Support of the Defendant's Joint Opening Claim Construction Brief." And, as represented by counsel, this is an amended version that was provided to the Court.

MR. BERL: And filed.

MR. SANDEL: And filed.

MR. BERL: Served.

BY MR. SANDEL:

Q. Now, if you would turn to paragraph 39 -- you may already be there.

A. I am there.

Q. You are there.

A. I am there.

Q. Great. And so the question which I'd

asked is whether these -- the claims that are presented in the chart in Claim 39 were from the '755 patent application. With the amended report in front of you, can you answer that question?

A. Yes, I can. The left-hand panel of that chart indicates that this was taken from Claim 31 of the '930 patent. And on the face of the '755 patent, it indicates that the '930 patent was the application number filed May 25, 1995, which issued as the '755 patent.

Q. And the '723 patent application which is referenced in the right-hand portion of the chart, that is, to your understanding, a different application?

A. I understand that's a different application.

Q. And you cite the Fletcher declaration, Exhibit 5, at 5, and the Fletcher declaration, Exhibit 6, at 5.

Let me ask you, did you review the -- were -- were you provided with the Fletcher declaration, Exhibit 5, and Exhibit 6?

A. I -- I was provided with the Fletcher

declaration, and I was also provided with the file history sections that this part of my declaration pertains to.

Q. Okay. And you -- you reviewed those in full?

A. I reviewed a significant portion of the -- of the file history surrounding these issues.

Q. Now, the claim that you have chosen to place in the chart is Claim 31; correct?

A. That's correct.

Q. All right. Did you examine Claim 32?

A. I did.

Q. Let me hand to you Exhibits 3, 4, and 5.

(Exhibit No. 3 was marked for identification.)

(Exhibit No. 4 was marked for identification.)

(Exhibit No. 5 was marked for identification.)

MR. SANDEL: And I'll also hand a copy of these to counsel.

BY MR. SANDEL:

J. Ravetch

Q. Exhibit 3 bears the Bates numbers BIMA0005639 through 42. Exhibit 4 bears the Bates numbers BIMA0005496 through 502. And Exhibit 5 bears Bates numbers BIMA0010885 through 92.

Now, doctor, are these the portions of the file history that you relied upon in forming your opinions expressed in -- starting at paragraph 39 of your report?

MR. BERL: Why don't you give him the Fletcher declaration so he can see what he's cited?

Q. So I'll represent to you that Exhibit 3 was presented in the Fletcher declaration as Exhibit 5, and what has been marked as Exhibit 5 was presented in the Fletcher declaration as Exhibit 6.

MR. SANDEL: I apologize. I may have made an error. While the -- it's easier to give him the Fletcher declaration --

MR. BERL: Right.

MR. SANDEL: -- I don't have a copy of it.

J. Ravetch

MR. BERL: Okay, you do now.

MR. SANDEL: Yes, I do.

BY MR. SANDEL:

Q. Let me help clarify.

A. Yes. What is the question?

Q. There isn't a question. I'm going to help clarify the documents --

A. Oh.

Q. -- you hold before you.

A. Thank you.

Q. What has been marked as Exhibit 3 --

A. Yes.

Q. -- was Fletcher Exhibit 7.

A. Okay, which is not referenced here. Okay.

Q. What you hold as Exhibit 4 --

A. Yes.

Q. -- was Fletcher Exhibit 5.

A. Yes.

Q. And what's before you as Exhibit 5 was Fletcher Exhibit 6.

A. Very good. Thank you.

Q. All right. Now if you would be so kind as to turn your attention to Exhibit 3 --

A. Yes.

Q. -- on the second page --

A. Yes.

Q. -- the second full paragraph, third sentence.

A. Yes.

Q. "The positive process steps in Claim 31 through 34 of the instant application and Claims 31 through 34 respectively of serial number 08/448723 are identical. The only difference in the claims is in the preamble, i.e., the intended use of the -- of the two processes. Since the actual process -- process steps of the two sets of claims are the same, the scope of the two sets is the claim -- is the same." Do you see that?

A. Yes, I do.

Q. Is it your understanding that the examiner, in addition to Claim 31, which you cite here, made the same rejection as to Claims 31 through 34?

A. That's what it says in this document.

Q. And that the positive process steps were contained in Claims 31 through 34?

A. The positive process steps are within that range of claims.

Q. Okay. Now, I understand it's your opinion that the positive -- the only positive process step -- steps that the examiner could have been referring to are "the produced by a host cell, transformed by a recombinant DNA molecule'; is that correct?

A. That's correct. That's my opinion.

Q. Would you turn to Exhibit 5. And in particular, to page 6.

A. Yes.

Q. Claim 32.

A. Yes.

Q. Does Claim 32 contain the process steps you've identified of producing by a -- "produced by a host, transformed by a recombinant DNA molecule"?

A. It does not.

Q. Does Claim 32 contain the step of administering a pharmaceutically effective amount of a composition?

MR. BERL: Objection.

A. It does. Doesn't say "step," but it

says "comprising and administering a therapeutically effective amount," yes.

Q. Does that same language appear in 31?

A. The language "administering a therapeutically effective amount of a composition comprising" appears in Claim 31.

Q. And if you would turn to Exhibit 4 and again to page 6 --

A. Yes.

Q. -- Claim 32 --

A. Yes.

Q. -- does Claim 32 of Exhibit 4 contain what you've identified as the process step "produced by a host, transformed by recombinant DNA molecule"?

A. The language "produced by a host cell, transformed by recombinant DNA molecule" is not found in Claim 32.

Q. Does it, in fact, contain a process step?

A. Does what contain a process step?

Q. Claim 32.

A. I'm not sure I can answer that question based on the materials you've given

me.

Q. It does contain the language "administering a therapeutically effective amount of a composition"; correct?

A. The words are found in that claim, yes.

Q. Now turning back to Exhibit 3 --

A. Yes.

Q. -- which is the office action by the examiner, and in particular, the portion that you quoted earlier, it says that "The positive process steps in Claim 31 through 34 of the instant application -- instant application and Claims 31 through 34 of serial number 08448732 are identical."

A. Yes, I see that.

Q. Why in your opinion do you believe the examiner is referring to what you've identified as process steps that appear only in Claim 31 and not a process step which appears in both Claim 31 and 32?

MR. BERL: Objection, lack of foundation. You can answer.

A. So there are several reasons. First

of all, it refers to Claims 31 through 34. Claims 33 and 34 are dependent on Claim 31 so therefore, he's referring to Claims 31, 33, and 34 by your construction at the very least.

It refers to process steps and not a process step. What you've pointed out in Claim 32 if, indeed, it is a process step is not process steps, so there's a multiple, multiplicity of process steps that the examiner is pointing to.

He also makes it clear that the positive process steps in these claims are identical. The only difference in the claims is in the preamble, and the -- the presumptive step that you're referring to in Claim 32 which is repeated in Claim 31 as well as 33 and 34 is in the preamble, as I understand the structure of the claim.

In addition, the administration of a therapeutically effective composition is not identical in all the claims. The words may be identical, but from a practical standpoint, administering -- as the patent teaches us, administering a therapeutically effective

amount for a viral disease is quite different than administering a therapeutic effective amount for cancer immunomodulation. And we know that because if we turn to the patent, it talks about what doses are required for the different types of applications that a interferon preparation might be put to. And it makes it clear that, while for viral treatment, brief exposure may be sufficient for antitumor therapy, long-term administration at different doses would be required.

So from all of those reasons, I believe it's quite clear that the examiner is referring to positive process steps, not a step. The only positive process steps, production and transformed, that meets that is -- that's not -- that's -- that's identical in all the claims is that step.

And finally, the rest of the file history which I reviewed relevant to this question demonstrated that cancellation of Claim 32 occurred. Claims 31, 33 and 34 were now the claims that were being considered, and the examiner issued the exact same rejection

that the claims were identical, except -- and they had the positive process steps.

So if 32 is taken out of the equation and the same language applies, my understanding therefore is that what the examiner was referring to in the document that you produced, Exhibit 4, is to the positive process steps of producing by a host and transformed by a DNA molecule.

Q. There was a lot to that answer. Let's unpack that just a little bit.

First, you mentioned they're not the same because, as you know, the dose for treating viruses is different than the dose for immunomodulation. The claims don't claim a particular dose, do they?

A. The claims -- these claims that we're discussing at this point?

Q. Correct.

A. Oh. These claims talk about a method treating either human viruses or a method of immunomodulation, administering a therapeutically effective amount. By definition, if it's therapeutically effective,

it has to have an activity that will have therapeutic benefit. And we know from the specification that those therapeutically effective amounts are different.

So yes, it does discuss dose by virtue of the fact that the specification talks about different doses that are therapeutically effective.

Q. Right. And it -- and it suggests having a therapeutically effective amount for a particular condition; correct?

A. Right. And these two conditions are different and therefore, the administrating -- administering language cannot be identical. You're administering different amounts. So that's not identical in the context of what the examiner said, that the only thing that's different here are the positive -- as -- as a preamble, because the positive process steps are identical --

Q. And --

A. -- so --

Q. -- when the --

A. -- administering can't be a positive

process step that's identical.

Q. And when the -- and when the examiner referred to Claim 32 as having the same steps, they were just wrong?

MR. BERL: Objection --

A. The examiner --

MR. BERL: -- misstates the record.

THE REPORTER: I'm sorry?

MR. BERL: Misstates the record.

THE REPORTER: Thank you.

A. The examiner doesn't refer to Claim 32. He doesn't call out Claim 32. We just read it. The examiner calls out Claims 31 through 34, which are the pending claims of this particular application. And in a subsequent rejection, after 32 has been canceled, Claims 31, 33 and 34 remain. And the language -- we can look at that if you have that. The language is the same, that these claims have the same positive process steps.

Q. All right. Well, let's stick to the material you actually cite in your report, which is the materials you have before you. And there, the examiner says Claim 31 through

34. That would include 33, would it not?

A. No, I -- I would -- I would no --

Q. Or 32, would it not?

A. Excuse me, counselor. No, I definitely talk about the remainder of the file history in paragraph 41. So this, 39, introduces the first statement by the examiner, but as one reads through the file history, as I have done, and -- and I say following this statement by the examiner, Biogen stated and made various amendments and also -- we didn't talk about that -- referred to the claims as reciting a positive process step.

So the additional amendments include cancellation of Claim 32, and the additional prosecution by the examiner rejected it with the same language.

So I think it's a simple logical conclusion that 32 is included in the range. And I'm not patent expert. I'm not presenting myself as such. I don't claim to understand the details of -- of proceedings in the Patent Office. But from a purely scientific standpoint, I would understand that 31, 33, and

34 are the subjects that are being discussed in terms of positive process steps.

MR. SANDEL: And with that, I think we need to change the tape.

THE VIDEOGRAPHER: Here marks the end of videotape number 3 taken in the deposition of Dr. Jeffrey Ravetch. Going off the record. The time on the video screen is 14:15 and 30 seconds.

(A recess was taken from 2:14 p.m. through 2:27 p.m.)

THE VIDEOGRAPHER: Here marks the beginning of videotape number 4 taken in the deposition of Dr. Jeffrey Ravetch. Going back on the record. The time on the video screen is 14:27 and 15 seconds. Please continue.

BY MR. SANDEL:

Q. Doctor, before we had to switch tapes we were discussing your reasons why you believe that the process steps referred to by the examiner were not the process of administering a therapeutically effective amount of the composition, and one of the reasons that you

gave me is that that language is contained in the preamble. Do you recall that?

A. Yes, I do.

Q. Now, if you could turn to Exhibit 3.

A. Exhibit 3.

Q. Exhibit 3, yes.

A. Yes, right, got it, examiner's statement. The examiner's statement, yes.

Q. The examiner there specifically identifies the difference in the preamble as being the intended use of the two processes; correct?

A. Yes.

Q. The examiner is not referring to the entire preamble and is not referring to the administration of a therapeutically effective amount of the composition, are they?

MR. BERL: Objection.

A. As -- for the reasons I gave before, as I understand the claim, speaking as one of skill in the art reading a claim, it would include the entire preamble, which is a method of treatment for a particular disease comprising administering a therapeutically

effective amount of a composition, which is the intended use of the -- of the two processes.

Q. The examiner specifically identifies what they saw as the difference in the preamble, did they not --

MR. BERL: Objection, form.

A. And -- and -- and I --

Q. -- i.e., the intended use of the two processes?

A. Right. And the intended use is treatment with therapeutically effective amounts, and those are different in the two claims. Both the -- the disease and the treatment are different.

Q. And you think that that's a -- a -- a more reasonable understanding, then, that Claim 31 is -- Claim 31 of Exhibit 5 is a method for immunomodulation and for Exhibit 4 is a method for treating human viruses?

A. Well, since --

MR. BERL: What -- what's the question?

Q. The question is: So you believe that your interpretation is a more reasonable

understanding than the possibility that the examiner is referring to the portion of the preamble in which it specifically sets forth the condition to be treated, that is, human viruses or immunomodulation?

MR. BERL: Objection, mischaracterizes the document.

A. Yeah, I -- I think my interpretation, looking at it as one skilled in the art, is more consistent with the entirety of the file history and subsequent rejections and statements by Biogen that would direct attention to the differences, which is the processes -- I'm sorry, which are the -- the -- the -- the shared steps, which are the two process steps.

Q. The shared steps as between Claim 31?

A. 31, 33, 34, as well as Claim 31 of an application that I referred to in paragraph 41 of my report.

Q. But not Claim 32, which does not contain the process steps that you referred to?

A. I don't make any comments on Claim 31. And my analysis, as you see here, is

focused on my understanding of the file history and the -- what a reasonable person would conclude when 32 was taken out of the prosecution and the same language of objection was used. It recited the same positive process steps, plural.

Q. You mentioned -- and plural is where we were going next. You mentioned plurality as being another one of the reasons that you believe your interpretation of the claim is correct. The examiner is referring to multiple claims in the rejection, are they not?

A. He's referring in document marked as Exhibit 3 Claims 31 through 34.

Q. And given that there are multiple claims being discussed, why is it not the case that the use of "plural" when discussing process steps is due to the fact that there are multiple claims being discussed?

A. I think from the subsequent file history you can -- you can reach the conclusion that I've reached, that the examiner's referring to the process steps within a claim, 31, or the dependent Claims 33 and 34. And

that was the understanding that I believe Biogen gave to the examiner's statement.

In paragraph 41, I cite to their characterization of Claim 31 from a different patent as having positive process steps, in plural.

So all of that combined, I think, is compelling to me that the steps that are being referred to by the examiner are the steps within the claim, as Claim 31, and that Claim 31 indeed has multiple steps, a produce step and a transform step at the very least, that are identical.

Q. So I want to understand this. You think that the word "transformed" as it appears in the claims of the '755 patent represent a process rather than a -- a description of the recombinant polypeptide; is that right?

A. Absolutely. Neither "produced" nor "transformed" describe the polypeptide. The polypeptide, as I've said many times, is defined by the amino acid sequence, and the amino acid sequence remains unchanged. Whether you're expressed in this cell or that cell, the

amino acid sequence is, in fact, a -- a constant.

So, for example, if you glycosylate the polypeptide, it's still a polypeptide with now amino acid sequence, now glycosylated. If it's folded, it's now a polypeptide that's been folded. If it's acetylated, lipidated, ADP ribosylated, phosphorylated, citrullinated, on and on, it's still a polypeptide. Right. So the "transformed" and "produced" language in no way defines a recombinant polypeptide.

Q. You mentioned, I believe, signal sequence. Now, if there -- there was a signal sequence, that would be removed depending on the host cell; correct? Whether the signal sequence was or was not removed would depend on the host cell?

MR. BERL: Objection.

A. The -- that's a processing step of the polypeptide. But the precursor polypeptide is still defined by the DNA sequence, whether it's a fusion DNA -- excuse me, a -- a fusion polypeptide as disclosed in the patent in many of the examples, or it initiates at a

particular amino acid subsequent to processing, the polypeptide is defined by the DNA. And the recombinant polypeptide can undergo not just signal sequence cleavage, it can undergo other processing steps.

It can undergo cleavages so that the precursor is generated so that you now have multiple chains that assemble and so on and so forth. Insulin, for example, expressed as a precursor will be processed. Factor 8 expressed as a precursor will be processed to generate different size molecules. However, the polypeptide is specified by the DNA that's been introduced into the cell, and that is a process that is being defined.

Q. Now, I understand that one of the -- moving away from the prosecution file history into the specification itself, you also rely on -- and this is in Claim 44 of your report -- your declaration.

A. Paragraph 44?

Q. Yeah. The use of the word "was transformed" in -- in the specification.

A. Uh-huh.

J. Ravetch

Q. So that you mention that the patent repeatedly states that certain strand of E coli was transformed by specific DNA molecule. And the next paragraph, you say these results demonstrate that transformation's a process performed upon the host. Right?

A. That's correct.

Q. Does the claim say "was transformed"?

MR. BERL: Objection.

Q. Look at Claim 1.

A. Yes, Claim 1. So the relevant section is "a recombinant polypeptide, produced by a nonhuman host, transformed by a recombinant DNA molecule." I mean, the only way the nonhuman host cell can produce this polypeptide is having undergone a transformation step. One of skill in the art --

Q. Let's just --

A. -- understands that transformation is an active event. It's a process.

Q. Well, let's answer my question, then we'll get to your statement. Does the claim say "was transformed"?

A. Well, the word "was" is not in the claim.

Q. Thank you.

Now, have you ever heard one describe a cell as a transformed cell?

A. The term "transformed cell" --- well, correctly used for bacterial cells and forgetting about the -- the oncologic implications of transformation for a moment, if -- we agree we can put that aside?

Q. Correct.

A. Okay, fine. So I'm not referring to -- if we're talking about DNA-mediated gene transfer, then a transformed cell or a transformed cell line is used routinely.

Q. And it's used to describe the cell and something that happened to the cell at some point?

A. It's -- it defines the process by which that cell has been phenotypically altered in a stable fashion.

Q. If I were to walk up to you and hand you a vial of cells and say, here are, you know, transformed X cells, you would understand

that at some point, although I might have done it, but at some point down the line, those cells underwent a process of transformation with some foreign DNA?

A. Correct.

(Exhibit No. 7 was marked for identification.)

BY MR. SANDEL:

Q. I've just handed you what's been marked Exhibit 7. I've also provided a copy to counsel. It is U.S. patent application number US2008/0206246A1. You are one of the named inventors on this patent application; correct?

A. Yes, I am.

Q. Do you mind turning to the claims of this patent? Let's go to Claim 7, which appears on page 12.

A. What -- what -- what -- what claim? Excuse me.

Q. Claim 7.

A. Claim 7. Sorry.

Q. Claim 7 is "the isolated polypeptide of Claim 1 produced from a recombinant source and lacking FAB region wherein said at least

one IGGFC region is glycosylated with two galactose moieties." And --

A. Uh-huh.

Q. -- my question is, in this claim, one which produced from a recombinant source, is that a process or a description of the polypeptide?

MR. BERL: Objection. Take as much time as you need to answer that question, obviously.

A. So I -- I have -- I have not reviewed this application. And I haven't seen the published form, actually, so thank you for showing it to me. I have not reviewed this application. And I believe it's actually still in prosecution. This is a publication of the application so I don't know the status of these various claims at this point and what has transpired.

But, once again, this -- as I answered in response to your earlier question, in the absence of having the opportunity to review the application and whatever proceedings have occurred in -- in the Patent Office, which

I imagine are still confidential, I would not be able to provide you with an -- an answer to your question.

Q. So sitting here today, as -- as the -- one of the named inventors -- the first named inventor of this patent application, you can't tell me whether you're claiming a isolated polypeptide or a process?

MR. BERL: Objection.

A. I thought the question was --

Q. Just looking at Claim 7.

A. I thought the question was actually a polypeptide produced by a particular process. And to answer your question, as I said, I would require enough time to review the patent as well as to look at whatever prosecution has occurred to determine what, in fact, is the -- the status of the various claims at issue. So I cannot address your question. It's certainly possible that -- that the claim refers to a polypeptide produced by a particular method and is providing no further description of the polypeptide, since the polypeptide is defined in Claim 1 with whatever properties it's being

given. But that would not be an appropriate answer without the opportunity to review this thoroughly.

Q. And I think I know your answer to this, but let me direct your attention to Claim 9, "an isolated polypeptide of Claim 1 derived from a cell line having an enhanced activity of creating alpha 2-6 linkages between at least one galactose moiety and respective terminal sialic acid in the protein's polysaccharide chain."

A. Uh-huh.

Q. Do you see that?

A. Yes, I do.

Q. And sitting here today, can you tell me, the term "derived from a cell line," continuing on, is that a description of the polypeptide?

A. I -- sitting here today, I can't answer your question. As I said in -- in reference to Claim 7, it -- it could be a process that is, in fact, used to produce this polypeptide and the polypeptide is defined earlier on, you know. This -- the general

subject matter of this invention, I can certainly talk about it related to the identification in natural IGG of a composition that conferred antiinflammatory activity. And recapitulating that activity in a recombinant molecule is one of the topics that we address in this -- in this publication -- sorry, in this patent application, which, of course, relates to publications that we've prepared as well. So, you know, it -- it is certainly possible that those claims are referring to the process by which one produces the recombinant polypeptide and certain properties that we identify earlier on. But without reviewing the entire application and prosecution, I can't be certain.

Q. Is it also possible that it's referring to characteristics of the polypeptide?

A. It's unlikely. Excuse me. It's unlikely, because we define the characteristics of the polypeptide in the patent as an FC sequence, and that has a defined amino acid sequence. And, once again, a polypeptide is an

amino acid sequence that can become subsequently modified. In this case, specific modifications confer specific biological properties but the polypeptide hasn't -- hasn't changed. So I'd have to read that more completely to be able to demonstrate what my best understanding would be.

Q. Now, in -- in -- in language, it is possible, of course, to use descriptions or phrases about processes which, in fact, are used to define the characteristics of an object; right?

MR. BERL: Objection.

Q. Let me give you an example.

A. Yes. I'm lost.

Q. All right. Fair enough. Let's -- let's take a -- a hypothetical claim. All right? How about a method for sweetening pancakes. All right? Comprising a -- pouring maple syrup made in Vermont over pancakes. Right? You understand that? All right.

A. Fine. I don't -- I don't --

Q. It's a hypothetical.

A. Yes, no, I'm -- I'm trying to

understand your hypothetical, and I get it, so right.

Q. The "made in Vermont" portion of that, all right, describes the type of syrup that is being used to sweeten the pancakes; right?

MR. BERL: Objection.

A. I mean, I -- what else do I know about this -- this process? I mean, distinguishing the process over maple syrup made someplace else and therefore their claim is -- is -- is being defined to a particular subset? You know, does the patent application provide me with guidance to understand what the terms, you know, are to mean to one of skill in the art? I'm not a pancake eater. I'm -- I say right now I'm not one of skill in the art so I think in this case, I can't even offer an expert opinion as one of skill in the art.

Q. Nor was I suggesting that you are an expert in pancakes. But in simple, everyday English, do you think that that -- this claim would require that somebody who wanted to sweeten their pancakes has to, before they do

it, travel to Vermont, collect sap from trees, boil it down to syrup, and then come back and sweeten their pancakes? Or is it enough that they have a jar that says "Vermont maple syrup," and they use that to pour on their pancakes?

MR. BERL: Was the "collecting sap from trees" in the claim or not? I'm lost.

MR. SANDEL: "Collecting sap from the trees --"

MR. BERL: And the claim is --

MR. SANDEL: -- is not --

MR. BERL: Okay.

MR. SANDEL: -- in the claim.

MR. BERL: Okay.

A. All that's in the claim is --

Q. We can --

A. -- "sweeten with maple syrup made in Vermont." And you're asking is "made in Vermont" a process?

Q. Correct.

A. Right. So --

MR. BERL: Objection.

A. So I can -- I can see a situation where this particular inventor has a, you know, a -- a world of prior art, people who have been sweetening their pancakes with Canadian maple syrup, and he wants to make sure that Vermont maple syrup is distinguished over the Canadian maple syrup. So it's not the maple syrup that's important but where it was made that's important.

So perhaps in his circumstance, "made in Vermont," which is a big deal to people in Vermont, they proudly proclaim "made in Vermont" on their logos, is not irrelevant. It is, in fact, a -- an -- an important part of the claim.

Q. Okay.

A. So the answer is, one needs to know more in order to understand how to construe that term, and that's exactly the case in this '755 patent. You need to know what the inventor tells you is the invention and what is discussed during the prosecution to inform an opinion, as I have, of what the claim terms would mean to one of ordinary skill. And I've

expressed my opinion they mean that it's a method of treatment of particular diseases by recombinant peptides prepared through a certain process.

MR. SANDEL: Go off the record.

THE VIDEOGRAPHER: Going off the record. The time on the video screen is 14:54 and 32 seconds.

(A recess was taken from 2:54 p.m. through 3:04 p.m.)

THE VIDEOGRAPHER: Going back on the record. The time on the video screen is 15:04 and 32 seconds. Please continue.

BY MR. SANDEL:

Q. Welcome back. Now, is there anything about your testimony today that you wish to correct or amend?

A. No. There's nothing.

MR. SANDEL: Then with that, I have no further questions.

THE VIDEOGRAPHER: Going off the record. The time on the video screen is 15:05 and 8 seconds.

J. Ravetch

(Discussion held off the record.)

THE VIDEOGRAPHER: Going back on the record. The time on the video screen is 15:05 and 35 seconds. Please continue.

EXAMINATION

BY MR. BERL:

Q. Good afternoon, Dr. Ravetch. I have a few questions for you. You were asked by counsel this morning about some consulting work you did in the past for Serono and Novartis. Do you recall that testimony?

A. Yes, I do.

Q. Can you approximate what amount of your income over the last 20 or so years has derived from consulting with Serono and/or Novartis?

A. I think for Serono it would be, you know, essentially nothing. It was probably a few hundred dollars back 20 years ago when I presented at their facility in Massachusetts.

For Novartis, somewhat more, but maybe -- it was at least ten years ago. And I think I was given about 25,000 a year for two

years, so that's the best of my recollection.

Q. And in the last decade, is that a significant portion of your income?

A. No, it's not.

Q. Okay. Do you have any relationship or have you had any relationship with Biogen or any subsidiary of Biogen?

A. Yes. I've -- I've had a relationship with an entity called Biogen Ventures, which is a venture investment arm of -- of Biogen. They invested in a startup company that I founded back in 2007.

Q. And was that a significant investment that Biogen Ventures made in your company?

A. You have to define "significant," but it -- it -- it was a minority position. There were four lead investors and they had a -- a small side investment. In their terms, a small side investment, right. I should point out that Virdante no longer exists so it's not a -- a consideration.

Q. Have you had any scientific contact or collaboration with -- with Biogen?

A. I -- I have colleagues at -- at

Biogen, immunologists in particular who I've over the years maintained good relationships with. I've been invited many times to Biogen's site in Cambridge. I've lectured, and I've spent the day in discussions related to antibody therapeutics and FC engineering.

Q. If you could take a look at your expert report, which is Exhibit 6, and in particular, in paragraph 24, which --

A. I'm sorry, exhibit -- Exhibit 1, I believe.

MR. SANDEL: Exhibit 1.

MR. BERL: Exhibit 6.

THE WITNESS: Oh, the revised.

MR. SANDEL: The revised.

THE WITNESS: Okay, the revised Exhibit 6, yes.

BY MR. BERL:

Q. You were asked about --

A. What -- what paragraph?

Q. Paragraph 24 on page 6. I -- I just wanted to clear up the record because I'm not -- I'm not sure it was clear. You were asked various questions about publications of

recombinant expression of human genes. Do you recall that?

A. Yes, I do.

Q. And were you testifying about what had been done by early 1980 or what had been done by 1981?

A. The statement in the report on paragraph 24, it was early 1980. I don't believe it includes 1981 citations.

Q. Have -- have you undertaken in connection with this report to determine what had been published between early 1980 and the end of 1981?

A. Not at the present time.

Q. If you could take a look at what I'll have the court reporter mark as -- 8? -- as Exhibit 8.

(Exhibit No. 8 was marked for identification.)

BY MR. BERL:

Q. For the record, Exhibit 8 is entitled "Expert Declaration of David Jackson." Have you seen this document?

A. Yes, I have.

Q. Do you understand this to be an expert declaration submitted by an expert on behalf of Biogen in this case relating to claim construction?

A. That's my understanding.

Q. And if you could turn to page 7 -- or page 4, excuse me, paragraph 7, do you see there's a section entitled "Level of One of Ordinary Skill in the Relevant Art"?

A. Yes, I do.

Q. Why don't you take a moment to review that paragraph.

A. I see that.

Q. Now, my question is: If that definition of the person of ordinary skill in the art were applied, would any of the opinions expressed in your expert report or in your deposition today change?

A. No, they would not.

Q. Now, you testified earlier today that you have made recombinant polypeptides yourself; is that right?

A. That's correct.

Q. And you're familiar with others

likewise expressing recombinant polypeptides?

A. I am.

Q. Are you familiar in your experience in the field with a situation in which the same person or entity prepares a -- a biological composition and then administers that composition to treat disease?

A. I am.

Q. And can you explain that a little more?

A. Well, for example, there are programs at the National Institutes of Health where they have investigators at the NIH who are investigating the biological properties of potentially promising new therapeutics, for example, in autoimmune disease or in cancer, and they are able to produce the recombinant molecules in order to do clinical trials with that material. So the same laboratory would be involved in designing the recombinant molecule, for example, and then the production that's done is under their supervision and the proteins that were obtained from that are administered to patients in clinical trials.

That's one of many examples where, quote, an investigator initiated clinical study.

Q. And are there other examples of the same person or entity preparing the biological composition and administering it to treat a disease?

A. So prior to the recombinant days of production, in fact, that was fairly routine that a -- a laboratory would have a -- a promising observation, the material that was identified was then produced, and -- under the laboratory or the entity's supervision, and that material was then used in a clinical study. And in some of the cell-based therapies that, in fact, are going on at the Rockefeller University, those precise parameters are in place where the same laboratory has people in the laboratory who are preparing various cellular preparations that are then administered to patients by other members of the laboratory for clinical studies.

MR. BERL: That's all the questions I have.

MR. SANDEL: I just have a couple

J. Ravetch

brief follow-up questions.

EXAMINATION

BY MR. SANDEL:

Q. Outside the context of clinical trials, are you aware of any instance in which the person administering the pharmaceutical is also the person who prepared the pharmaceutical?

A. I'm not quite understanding the distinction. These are using approved drugs?

Q. Correct.

A. So if a drug is approved, you would be able to potentially obtain it commercially, in which case you would obtain the material and perform the clinical study. And there's lots of examples of that, of course. In the IVIG world, you know, there's an immense interest, for example, in using this preparation for treating Alzheimer's disease, and investigators at Cornell use the hospital grade IVIG and perform their clinical studies.

Q. I understand. Sorry. Perhaps I misspoke, or I wasn't clear. Outside of the context of clinical trials, just treatment of a

patient, have you yourself as a physician ever treated a patient outside the context of clinical trials with a recombinant product that you yourself made?

A. Outside of the context of an investigation into --

Q. Correct.

A. -- a clinical pathway, I personally don't have any experience in that -- in that application.

Q. All right. Are you aware of any situations outside of the context of clinical trials in which a physician has treated a patient with a recombinant product which they themselves produced?

A. I know of one interesting example. It has to do with the -- changing the formulation of a recombinant product where a -- a formulation was developed for a particular therapeutic area and the physicians themselves took it upon themselves to change the formulation by diluting the product dramatically and then using it in a new application.

So that's where the investigator has, in fact, taken the product, the recombinant product, and essentially manufactured a new version of it. Interestingly, in that -- that particular case, the results were so -- were so satisfactory, the dosing being 1/100 the dosing, and the formulation being different, that the manufacturer now obtained a new product line based on that new formulation. So the answer is it -- it does happen.

Q. All right. And in the example you just gave, the physicians weren't -- they didn't transform the cells or produce the recombinant polypeptide; correct? They diluted --

A. They reformulated the recombinant polypeptide. But it was a new preparation, and sufficiently new that it was patented and considered to be a -- a new product species that was now, you know, used in different applications. So, you know, similar, different, whatever.

Q. So going back to my original questions, did -- are you aware in any instance

in which a physician treated a patient with a recombinant polypeptide which they themselves had produced?

A. You know, I'm not --

MR. BERL: Outside the context.

Q. Outside the context of clinical trials, yes.

A. Right. I -- no, I'm not.

Q. In your experience as a physician, does the average physician have the equipment and facilities in their office by which to make a recombinant polypeptide?

MR. BERL: Objection, lack of foundation, vague.

A. So it would depend upon what type of physician. Academic physicians in tertiary medical centers often have research facilities, research laboratories. My colleagues at St. Jude's, for example, have a GMP manufacturing facility which is at their disposal to do exactly this, to make clinical grade material for clinical investigation. But it is usually -- I don't know of a -- of a case otherwise -- in the context of an investigation

into a particular pathway and -- and perhaps treatment.

I mean, it -- it's an interesting question because I'm -- it -- it -- it comes up not infrequently where a particular manufacturer has a recombinant product which, for whatever reasons, is not progressing through clinical approval by the FDA, and those materials are obtained by academic groups to continue the process of manufacturing and clinical studies.

Q. But that's within the context of the clinical studies; correct?

A. It -- it's usually preapproval status that I'm aware of.

Q. And you're not aware of any instance of a -- an approved drug, approved recombinant -- approved recombinant polypeptide being administered by the doctor who also then went to the lab and made the recombinant --

A. So -- so I think --

Q. -- polypeptide?

THE REPORTER: Made the recombinant?

MR. SANDEL: Polypeptide.

A. The best answer is I haven't investigated that question. Certainly in the case of clinical trials I'm well aware of that, but for the case of approved drugs, you know, I'm thinking of colleagues in other countries where manufacturing and clinical -- of -- of -- of clinically approved drugs, in fact, can occur in a -- a different context. So I'd have to reserve answering until I've had a chance to actually explore that question.

Q. Now, you -- you're a practicing physician; correct?

A. Practicing? No, I haven't practiced --

Q. Oh.

A. -- in a while.

Q. You're a member of the department of oncology; is that right?

A. Not for a while now. When I was at Sloan-Kettering, I was a member of the clinical hematology service. But I am a physician scientist who has spent his career in basic research and clinically relevant applications.

Q. Have you ever had an opportunity to treat patients?

A. I have.

Q. Ever treat patients with a recombinant protein or polypeptide?

A. Yes.

Q. What recombinant polypeptides or proteins have you used?

A. Mostly antibody therapeutics. Sorry. Mostly antibody therapeutics, Recombinantly prepared antibody therapeutics for various oncologic indications, for example, as far as --

Q. Herceptin?

A. Herceptin, Rituximab are some of the molecules that I've published on and have, in fact, used in patients.

Q. And in instances where you treated a patient with Herceptin, did you yourself go and make the -- the Herceptin prior to administering it to the patient?

A. I did not.

MR. SANDEL: I have no further questions.

J. Ravetch

MR. BERL: No further questions.

THE VIDEOGRAPHER: Thank you. Here marks the end of videotape number 4, also marks the end of today's proceeding in the deposition of Dr. Jeffrey Ravetch. Going off the record. The time on the video screen is 15:22 and 3 seconds.

(Deposition adjourned at 3:21 p.m.)

_____

Dr. Jeffrey V. Ravetch

SUBSCRIBED AND SWORN TO BEFORE ME

THIS _____ DAY OF _____, 2011.

_____

(Notary Public)

My Commission expires: _____

C E R T I F I C A T E

DISTRICT OF COLUMBIA:

I, MARY ANN PAYONK, CRR-RDR, CBC, CCP, CLR, shorthand reporter, do hereby certify:

That the witness whose deposition is hereinbefore set forth was duly sworn, and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of September, 2011.

_____

MARY ANN PAYONK, CRR-RDR, CBC, CCP, CLR

Shorthand Reporter

---------- I N D E X ----------



---------- E X H I B I T S ----------

NAME OF CASE: In Re: Biogen '755 Patent
DATE OF DEPOSITION: August 30, 2011

1. To clarify the record.
2. To conform to the facts.
3. To correct transcription error.

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JEFFREY V. RAVETCH

SUBSCRIBED AND SWORN TO BEFORE ME
THIS _____ DAY OF _____, 2011.

_____
(Notary Public)
My Commission expires: _____